REMARKS

Claims 1-74 were previously canceled, and 75-147 are pending for the Examiner's consideration. Claims 75, 85, 86, 90, 91, 134, 136, 138 and 143 are amended herein. Applicants respectfully submit that these amendments introduce no new matter and these amendments are supported by the previously pending set of claims and have been made to clarify applicants invention. Any canceled subject matter is without prejudice or disclaimer and applicants reserve that right to file one or more continuing applications.

Rejections Under 35 U.S.C. § 103

Vinson *et al.* ("Vinson")

Claims 75-147 were rejected under 35 U.S.C. § 103 as obvious over Vinson *et al.* ("Vinson") based upon the Examiner's allegation that Vinson discloses that black tea whose main ingredients are theaflavins significantly improves the lipid provide of hamsters. From this disclosure, the Examiner concludes that it would have been obvious to isolate the theaflavins and feed them to humans to improve lipid profile.

Applicants respectfully traverse this rejection and wish to point out that the claims are directed to a method of reducing LDLs while not significantly reducing HDLs comprising administering a composition comprising an isolated mixture consisting essentially of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate or a composition consisting essentially of a mixture of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate or a daily dosage composition for administration, which comprises such mixtures and compositions of the four recited theaflavins in a therapeutically effective amount and for a time period sufficient to reduce the LDL while not significantly reducing the HDL over the time of administration.

Applicants wish to direct the Examinr's attention to Attachment 1, which is a single legal size sheet from the USDA, as known as Bhagwat *et al.i,* entitled "Flavonoid composition of tea: Comparison of black and green teas. Specifically, applicants direct the Examiner to Table 3 in which black tea, dry leaves, decaffeinated and brewed is compared with the corresponding type of green tea. From Table 3, of this publication, it is clear that theaflavins is not the "main ingredient" of black tea. In fact, there is almost 10 times more thearubigins, and almost 6 times more catechins than theaflavins in dry black tea leaves. Additionally, dry green tea leaves have

between three and four times more catechins than dry black tea leaves and almost one hundred times less theaflavins than dry green tea leaves. (See Attachment 1). Thus, dry black tea leaves contain the following flavonoid subclasses in the most to least prominent order: thearubigins > catechins > theaflavins > flavonols, whereas dry green tea leaves contain the following flavonoid subclasses in the most to least prominent: catechins >flavonols > thearubigins > theaflavins. Although theaflavins are the unique composition in black tea, there are other unique compositions in black tea as well, such as theabrownin and thearubigin. Therefore, considering the disclosure of Vinson alone, one skilled in the art could not have concluded the theaflavins could be isolated and would provide healthy effects of one of black tea's ingredients, theaflavin, on the plasma lipid profile.

Additionally, the specification of the present invention on page 1 in the Background section, lines 6-8, discloses that "typically, the concentration of theaflavins in black tea is between about 0.4-1.8% by weight with the concentration of theaflavins in green tea usually being far less."

Applicants submit that Vinson discloses that although the plasma lipid profiles were significantly reduced by both black and green teas, green tea was significantly more effective than black tea. On page 45, first column, the results are provided for the effect of black and green teas, and show that green tea is significantly better than black tea with respect to cholesterol, HDLs, triglycerides and atherogenic index. Additionally, page 44, first column of Vinson discloses that "catechins have been found to be the most potent group of antioxidants for inhibiting *in vitro* lower density lipoprotein oxidation by cupric ion." Thus, if one skilled in the art were reviewing Vinson and knew that both black and green teas lowered plasma lipid profiles and that green tea was significantly better with respect to moving lipid profiles in the correct direction, one skilled in the art would be motivated to select green tea to treat humans to improve lipid profiles and not black teas. This is particularly so because Vinson also identifies that cathechins are the most potent group of flavonoids to lower LDL oxidation and black tea contains lower amounts of catechins than green teas. Additionally, it is known that green tea contains low amounts of theaflavins, i.e., lower amounts than black tea, as can be determined by Attachment 1. Therefore, applicants submit that one would not be motivated by Vinson to use an isolated mixture of theaflavins from black tea to obtain a better plasma lipid profile. But rather one skilled in the art would consider which components in green and black teas are common and

which component(s) green teas contained more of in comparison to black teas, and then select those component(s) to use to treat humans to lower lipid profiles. As theaflavins are present in small amounts in dry green tea leaves, the selection of theaflavins to treat humans to lower lipid profiles would not be an obvious choice based on the disclosure of Vinson and the amounts of flavonoid subclasses present in black and green teas.

Applicants submit that in view of these arguments and supporting USDA document, it would not be obvious and there is no motivation in view of Vinson to isolate a mixture of theaflavins from black tea to administer to a human subject to lower LDLs without significantly reducing HDLs. In view of these arguments and supporting documents, it is requested that this rejection be withdrawn.

Vinson *et al.* ("Vinson") in view of Ishikawa *et al.* ("Ishikawa")

Claims 75-147 were rejected under 35 U.S.C. § 103 as obvious over Vinson in view of Ishikawa. The Examiner alleges that Vinson is applied as above in regard to disclosing that black tea, whose main ingredients are theaflavins, improves lipid profiles of hamsters, and that Ishikawa discloses that the addition of individual theaflavins to plasma *in vitro* increases the lag time before initiation of LDL oxidation. The Examiner concludes that the combination of these *in vitro* and hamster studies of black tea and its main ingredient, theaflavin, points to the use of theaflavins to improve lipid profiles.

Applicants respectfully disagree with the Examiner's conclusions to combine these two references. Firstly, as argued above, Vinson does not suggest to the skilled person that theaflavins from black tea is the ingredient responsible for improving lipid profiles in humans. Therefore, applicants submit that Vinson is not a proper primary reference in an obviousness rejection alone or in combination with Ishikawa to reject the pending claims which require administering an isolated mixture of the four claimed theaflavins which reduces LDLs while not significantly reducing HDLs in a subject. The Examiner cites Ishikawa, but applicants submit that Ishikawa is directed to studying theaflavins as an antioxidant. The Examiner has erroneously concluded that since theaflavins inhibit LDL oxidation, then theaflavins must lower LDL levels and provide a good plasma lipid profile. Applicants wish to point out is that the pending claims do claim to inhibit LDL oxidation by administering theaflavins but rather the pending claims are directed to administering an isolated mixture of the four claimed theaflavins

as the only active LDL lowering component. Inhibition of LDL oxidation and lowering LDLs are two different mechanisms and the Examiner has not shown that inhibiting LDL oxidation results in lowering LDL plasma levels without significantly reducing HDLs. The Examiner has not provided this relationship.

In support of applicants' position, applicants herewith provide a scientific publication by Diepeveen *et al.* (See Attachment 2) in which the effects of atorvastatin and vitamin E (α-tocopherol) were studied on lipoproteins and oxidative stress. The results section on page 438, second column, summarizes the study basically supporting applicants' position that inhibition of LDL oxidation does not result in the lowering of LDLs in the plasma. This section of the publication states that atorvastatin alone reduced total cholesterol, triglycerides, LDLs, apolipoprotein B and levels of oxidized LDL but had no influence on LDL oxidisability. When vitamin E was added, it had no effect on the lipid profile but decreased *in vitro* LDL oxidizability. These results support applicants' position that the effect of inhibition of LDL oxidation does not necessarily result in the lowering of LDLs in the plasma.

Additionally, Ishikawa is speculative as noted at the end of the abstract on page 261 and on page 265, second column, where it is stated that maybe tea flavinoids may have favorable effects in ameliorating artherosclerosis. Therefore, in view of all of the arguments made above in regard to Vinson, Ishiwaka does not cure the defects of Vinson or disclose that theaflavins lower LDL levels while not significantly reducing HDL levels. For all of these reasons, it is requested that this rejection be withdrawn.

Vinson *et al.* ("Vinson") in view of Leung *et al.* ("Leung")

Claims 75-147 were rejected under 35 U.S.C. § 103 as obvious over Vinson in view of Leung. The Examiner alleges that Vinson is applied as above in regard to disclosing that black tea, whose main ingredients are theaflavins, improves lipid profiles of hamsters, and that Leung provides a similar disclosure to Ishikawa and found the same results. The Examiner concludes that the combination of the references suggests the hypolipidemic activity of the theaflavins.

Leung's teaching that oxidation of LDLs is indicative of lowering of LDLs is faulty as argued above for Ishiwaka. For all of the reasons set forth above in regard to the inapplicability or disclosures in Vinson and Ishiwaka, and also because Leung does not cure any of the defects of Vinson, and it is requested that this rejection be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed or rendered moot. The Examiner has failed to make a *prima facie* case that the claimed methods of administering a composition that comprises an isolated mixture consisting essentially of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate and the specific composition that results in the lowering of LDLs while not significantly reducing HDLs in a human subject is obvious over the cited prior art alone or in combination.

Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,
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